REMARKS

Applicants thank the Examiner for the courtesy of a telephonic interview with Applicants' representative on November 13, 2006. The proposed amendments to the claims were discussed during the interview and the Examiner is thanked for her helpful suggestions.

Claims 1-4, 6-10, 12 and 15-33 are pending in the application. Claims 14-22 and 30-32 are withdrawn from further consideration without prejudice. Claims 1, 2, 6-10 and 23 have been amended. Claim 27 is canceled. Support for the amendments to the claims can be found throughout the originally filed specification and claims. Specifically, support for the amendments to claim 1 can be found, for example, at page 2, lines 23-34, support for the amendments to claim 8 can be found, for example, at page 2, lines 23-34, support for the amendments to claim 9 can be found, for example, at page 68, line 1, support for the amendments to claim 10 can be found, for example, at page 31, line 23, support for the amendments to claim 23 can be found, for example, in original claim 27 and at page 72, lines 17-20. Amendments to claims 2, 6 and 7 are merely clerical to clarify the claimed invention. No new matter has been added.

Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and has been done solely to more particularly point out and distinctly claim the invention, to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Applicants traverse the rejections and respectfully request reconsideration in light of the amendments and remarks.

Rejection of Claims 1-4, 6-10, 12, 23-29 and 33 under 35 U.S.C. 112 second paragraph

Claim 1-4, 6-10, 12, 23-29 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. As discussed during the telephonic interview with the

Examiner, claims 1, 2, 6, 7, and 23 have been amended to clarify the claimed invention. Accordingly, the Examiner is requested to withdraw this rejection.

Rejection of Claims 1-4, 6-10, 12, 23-29 and 33 are rejected under 35 U.S.C. 103(a)

As amended, claims 1-4, 6-10, and 12 are directed to a method for organ augmentation that requires *transiently* transfecting a population of cells with a plasmid encoding a VEGF angiogenesis modulating agent. These *transiently* transfected cells are then suspended together with a second population of a different cell type, and then *injected* into a target tissue region where the cells will transiently express the angiogenesis modulating agent and induce assimilation and differentiation of cells in the target region. As amended, independent claim 1 (and claims dependent thereto), recite the steps of "selecting a first population of cells from the transfected cells, which contain the VEGF encoding plasmid and *transiently express the VEGF* angiogenesis modulating agent, selecting a second population of cells, wherein the *second population of cells comprises cells of a different cell type than the first population*, suspending the first population of cells and the second population of cells in an *injectable polymer matrix*; *injecting the polymer matrix* into a target tissue region where the first population of cells will express the VEGF angiogenesis modulating agent."

As amended, claims 23-26, 28, 29, and 33 are directed to a method for augmenting organ function comprising "culturing at least a first population of cells on a matrix material to produce an organ construct, *transiently transfecting* a second population of cells with a plasmid encoding an angiogenesis modulating agent, wherein the second population of cells comprises cells of a different cell type than the first population, wherein either the first or second population of cells comprises *myoblasts*; and implanting the organ construct and the transfected cells *in vivo* at one target site to replace or augment organ function, such that the transfected cells *express the angiogenesis modulating agent for less than about 3 weeks*."

Claims 1-4, 6-10, 12, 23-29 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton *et al* (US 2003/0007954), in view of Lu *et al.* (Circulation, 2001), Atala *et al.* (US Patent 6,479,064), and Penn et al (US 2004/0161412 A1, 60/405,274

and 60/424,065). Claim 27 has been canceled. Applicants traverse this rejection. For each of the following reasons, Applicants respectfully disagree and request withdrawal of this prior art rejection.

Naughton *et al.* (US2003/0007954) primarily focuses on producing a *three-dimensional* cell culture system. The salient feature of Naughton *et al.* is to use stromal cells to create a *three-dimensional* stromal support system by culturing the stromal cells on synthetic polymers that can be *implanted or attached* (*See* paragraph [0001]). While the Naughton reference discloses that the framework can be made from a variety of materials, the reference specifically recites that these material are woven into a *three-dimensional* framework (*See* paragraph [0033]). From the teachings in Naughton *et al.*, the skilled artisan would conclude that a *three-dimensional* stromal matrix is an essential aspect of the cell culturing system. Therefore, Naughton *et al.* does not provide the necessary motiviation for the skilled artisan to search for *an injectable polymer matrix*, as required by amended independent claim 1 and further defined in dependent claims 2-4, 6-10, and 12.

In addition, while the Naughton reference teaches cells which have been genetically-engineered to produce exogenous gene products that promote angiogenesis, Naughton *et al.* clearly teaches that the "genetically-engineered stromal tissue may serve as a gene delivery vehicle for *sustained* release of angiogenic factors in vivo." (See, paragraph [0047]) Naughton *et al.* disclose the use of constitutive, tissue-specific, and stimuli-specific expression in order to achieve *sustained* release at the desired site. However, Naughton does not teach or even suggest *transient expression* of the angiogenic factor, as recited in claims 1-4, 6-10, 12, 23-26, 28-29 and 33.

The deficiencies of the Naughton reference are not overcome by the combination with Lu *et al.* (Circulation, 2001), Atala *et al.* (US Patent 6,479,064), and/or Penn *et al.* Fundamentally, before the Naughton reference can be combined with Lu *et al.*, Atala *et al.*, and/or Penn *et al.*, there must be some motivation to do so. The Examiner assumes such a motivation, but, in fact, no such motivation can be found in the Naughton reference. There is no identification of any problem (e.g., inadequate cell differentiation, problems with implantation, or hemangiomas,

hemorrhages, and enhancement of tumor angiogenesis) in the Naughton reference. Naughton *et al.* is simply directed to promoting blood vessel formation through the implantation or attachment of a three-dimensional stromal tissue that "may serve as a gene delivery vehicle for *sustained* release of angiogenic factors" (paragraph [0047]). Absent any appreciation of a better system, i.e., one for injecting instead of implanting the cells, and not recognizing that chronic or sustained expression of an angiogenic factor could be detrimental, there is simply no motivation for one skilled in the art to go looking for an ***undifferentiated population of cells***, an *injectable* polymer matrix, and a *transient* expression system, or other features and parameters of the claims that are not disclosed by Naughton *et al.*

Furthermore, the secondary references do not remedy the deficiencies in Naughton *et al.* as described below.

The Examiner cites Atala *et al.* (US Patent 6,479,064) for the disclosure of "other scaffold material." However, Atala *et al.*, similar to Naughton *et al.*, also describes how to prepare artificial organ constructs using *three-dimensional* scaffolds seeded with endothelial cells. These endothelial cells produce a vascular system that supports the growth of other cell populations. Atala *et al.* teach that these constructs can be ***implanted*** in a subject (Column 3, lines 32). Accordingly, Atala does not teach the use of an ***injectable polymer matrix*** as required by independent claim 1, and dependent claims 2-4, 6-10, and 12.

The Lu *et al.* reference discloses a method for delivery of VEGF using *implantable* bioartificial muscle (BAM) tissues made from genetically engineered myoblasts. The Lu *et al.* reference discloses the use of myoblasts as the sole cell population used in producing the bioartificial muscles. Since there is no suggestion in the Naughton reference that the disclosed cell types are not satisfactory, there is no motivation for one skilled in the art to look for other cell populations. It is improper to reconstruct the patentee's claimed invention from the prior art by using the patentee's claim as a blueprint. Furthermore, even if Naughton *et al.* is combined with Lu *et al.*, the salient features of independent claims 1 and 23, such as an *injectable* polymer matrix or a *transient* expression system, are not disclosed.

In addition, there is no motivation to combine the teachings in Naughton *et al.* with that of Penn *et al.* On page 8 of the Office Action, the Examiner states that:

> "While Naughton et al does not provide details on the transfection of the cells with VEGF, at the time the invention was made, means of transfecting cells, including myoblasts, with plasmids encoding VEGF were know in the art. See, for example, Penn et al."

Naughton specifically teaches "genetically-engineered stromal tissue may serve as a gene delivery vehicle for *sustained* release of angiogenic factors in vivo." (See paragraph [0047]). As discussed above, Naughton *et al.* disclose the use of constitutive, tissue-specific, and stimuli-specific expression in order to achieve *sustained* release at the desired site. Thus, Naughton *et al.* teaches away from *transient expression* of angiogenic factors. Accordingly, one skilled in the art with knowledge of Naughton et al. would no motivation to search for a *transient expression* system, as required by claims 1-4, 6-10, 12, 23-26, 28-29 and 33.

In summary, the Office Action rationalizes a case of obviousness by stating that the Naughton reference discloses a method for treatment of ischemic tissue and that the specifics of the claimed invention would be obvious to one skilled in the art. Without any suggestion or motivation in the prior art, it is improper to reconstruct the patentee's claimed invention from the prior art by using the patentee's claim as a blueprint.

For all the reasons recited above, it is clear that none of the cited references disclose or suggest the method of the present invention, that there is no motivation to combine these references, and that even if combined they do not disclose or suggest the method of the present invention. Thus, these references fail to disclose or suggest every element recited by independent claim 1 and 23. Because every limitation of an independent claim is imported to dependent claims, claims 2-4, 6-10, 12, 24-26, 28-29 and 33are also allowable. These dependent claims further define the allowable subject matter recited by claims 1 and 23. Applicant, therefore, respectfully requests that the Examiner withdraw all rejections.

Rejection of Claims 23, 25, 26, 29 and 33 are rejected under 35 U.S.C. 103(a)

Claims 23, 25, 26, 29 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meana *et al* (Burns, 1998), in view of Andree *et al.* (WO 01/89593). Applicants respectively transverse this rejection.

As amended, independent claim 23, and claims dependent thereto, recites "transiently transfecting a second population of cells with a plasmid encoding an angiogenesis modulating agent, wherein the second population of cells comprises cells of a different cell type than the first population, wherein *either the first or second population of cells comprises myoblasts*". Support for this amendment can be found in originally filed dependent claim 27.

Neither Meana *et al* (Burns, 1998) nor Andree *et al.* (WO 01/89593) teaches or suggests the use of *myoblasts* as one of the two populations of cells. Meana *et al* describes a *keratinocyte* culture system on a dermal equivalent that can be used in skin wound closure. Andree *et al.* describes transfection of *keratinocytes* for skin repair. Accordingly, none of the cited references disclose or suggest the method of the present invention. Therefore, even if combined they still do not disclose or suggest the method of the present invention. Thus, these references fail to disclose or suggest every element recited by independent claim 23, and dependent claims 25, 26, 29 and 33.

For all the forgoing reasons, the references alone, or in combination fail to arrive at the claimed invention. Accordingly, the Examiner is respectively requested to withdraw the obviousness rejection over claims 1-4, 6-10, 12, 23-26, 28-29 and 33.

CONCLUSION

In summary, the above-identified patent application has been amended and reconsideration is respectfully requested for all the reasons set forth above. In the event that the amendments and remarks are not deemed to overcome the grounds for rejection, the Examiner is kindly requested to telephone the undersigned representative to discuss any remaining issues.

Respectfully submitted,

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